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ScienceDirect
Journal of Forensic and Legal Medicine 15 (2008) 483–488
JOURNAL OF FORENSIC AND LEGAL MEDICINE
www.elsevier.com/jflm

Original Communication

The relation between the blood benzodiazepine concentration and performance in suspected impaired drivers

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Received 21 November 2007; received in revised form 25 February 2008; accepted 9 April 2008
Available online 13 June 2008

Abstract

Several experimental studies have shown a negative influence of benzodiazepines on driving skills. The objective of this study is to study the relationship between the blood concentration of benzodiazepines and the influence on performance in field sobriety tests.

A retrospective case file evaluation was conducted to select cases of drivers, tested positive for benzodiazepines only in the period from January 1999 to December 2004. Drivers were grouped into the categories sub therapeutic, therapeutic or elevated concentrations. The outcome of the tests (walking, walking after turn, nystagmus, Romberg's test, behavior, pupils and orientation) was binomial. A Chi square test was used to assess differences in proportions of the categorized cases.

In total 171 cases were included. Observations of behavior ($n = 137$; $p < 0.01$), walking ($n = 109$; $p < 0.01$), walking after turn ($n = 89$; $p = 0.02$) and Romberg's test ($n = 88$; $p < 0.05$) were significantly related to the benzodiazepine concentration. There was no significant relation between benzodiazepine concentration and effect on pupil size, nystagmus or orientation.

The results of our study indicate a relation between the concentration of benzodiazepines and the results of some performance tests. More effort is needed to standardize the tests and to determine the sensitivity and selectivity of the tests for benzodiazepines.

Keywords: Benzodiazepines; Blood concentration; Standardized field sobriety tests; Performance

1. Introduction

Several experimental studies have shown a negative influence of benzodiazepines on driving skills.[1–3] In addition, epidemiological studies have shown an association between benzodiazepine use and accident risk although the results of those studies have not always been consistent. Some studies suggest a relationship between blood concentrations of benzodiazepines and accident risk.[4,5] Until now, little information is available about the relation between blood concentration of benzodiazepines and the influence on standardized field sobriety tests. A study of Bramness et al.[6] suggested a dose-dependent impairment and as a consequence increased accident risk by benzodiazepines.

In The Netherlands, a suspicion of driving under the influence of psychoactive substances other than ethanol is obtained by deviant driving behavior or by observations from the police. A blood or urine sample can be taken from the driver by a physician and sent to the Netherlands Forensic Institute (NFI) by the police officer for toxicological analysis. On the request form for toxicological investigation, information should be filled in concerning performance of the driver while walking on line, walking on line after turn and standing on one leg for 30 s with eyes closed (Romberg's test). In addition observations concerning orientation (in time, place and person), nystagmus, behavior and pupil size are requested. The

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doi:10.1016/j.jflm.2008.04.002

performance of field sobriety tests is not required for legal purposes at this moment, but when performed, the results can be used to detect signs of impairment possibly related to the use of psychoactive substances which may result in the decision to take a blood sample.

The results of the toxicological analysis and an interpretation of the results with regard to driving performance are returned to the police. For ethanol in blood a legal limit is in force, based on the well established relationship between blood alcohol concentration and accident risk.[7] For other substances, no limits are laid down in the Dutch Road Traffic Act.[8] The police report with the toxicological report is sent to one of the nineteen district courts in The Netherlands. Depending on the case, prosecution may involve a single judge chamber (police judge) or a full bench of three judges (more serious cases). All information relevant to the case is filed.

The legal procedure could be simplified if legal limits were available for other substances than ethanol.[9] However, for benzodiazepines and other psychoactive substances, more information about the relationship between dose, blood concentration and effect is needed to establish limits indicating impairment that are incompatible with safe driving behavior. The objective of this retrospective case file evaluation is to study the relationship between the blood concentration of benzodiazepines and the influence on performance in field sobriety tests on drivers, who tested negative for alcohol and other psychoactive substances.

2. Methods

2.1 Study population

A retrospective review of the database of the Department of Toxicology, NFI was conducted to select cases of drivers suspected of driving under the influence of benzodiazepines only in the period from January 1999 to December 2004.

Cases were selected in which both a drug screening and a specific analysis by using high performance liquid chromatography in combination with UV diode array detection were performed with positive results for benzodiazepines, zopiclone or zolpidem only. The analytical strategy and methods used in forensic case work at the NFI have been described elsewhere.[10] The drug classes included in the screening were opiates, cocaine, methadone, amphetamines, benzodiazepines, barbiturates, cannabinoids and tricyclic antidepressants. In case of self-declared or suspected use of other psychoactive substances a more extensive screening was performed. The estimated cutoff value for benzodiazepines is around 0.01 mg/L for all benzodiazepines. Cases were excluded if the alcohol concentration was higher than the legal limit (i.e. 220 μg/L breath or 0.5 mg/mL blood). If neither an evidential alcohol breath test nor a blood alcohol test was performed, it was assumed that the driver passed the preliminary breath test or that there was no suspicion for alcohol use and that the alcohol concentration was lower than or equal to the legal limit. Data collected, relevant to this study were case identification numbers, age and gender of the driver, relevant toxicological data (analytical results, self-declared or suspected drug use) and the results of the field sobriety tests performed (i.e. walking, walking after turn, nystagmus, Romberg's test, behavior, pupils, orientation).

Approval from the Board of prosecutors-general, head of the prosecution service was obtained to perform this study.

2.2 Blood concentrations

Reference plasma or serum concentrations of the benzodiazepines detected were derived from literature.[11–13] However, the NFI measured the concentrations of benzodiazepines in whole blood. In general, the plasma to whole blood ratio has been published for many substances. With respect to benzodiazepines, the plasma to whole blood ratios has been published only for a limited number of substances (i.e. alprazolam, diazepam, nordazepam, oxazepam, temazepam, zopiclone).[12,14] For these compounds, reference plasma concentrations were converted to whole blood concentrations. In all other cases, plasma concentrations were defined to be equal to whole blood concentrations.

In order to relate the measured blood concentrations to the reference concentrations in blood, the measured values were expressed as the proportion of the average therapeutic concentration. This means that the measured blood concentration of a substance was divided by the mean of the lower and upper limit of the therapeutic range as mentioned in Table 1. If more than one substance (parent drug or metabolite) were detected in one blood sample the proportions were added up. The sum was grouped into one of the three mutually exclusive categories (a) sub therapeutic concentrations (sum lower than or equal to 0.35) (b) therapeutic concentrations (sum 0.35–1.65) or (c) elevated concentrations (sum higher than 1.65).

The thresholds of 0.35 and 1.65 are based on the ratios of the lower limit of the therapeutic range to the mean therapeutic concentration for all substances mentioned in Table 1 (mean 0.35; median 0.40; range 0.00–0.81) and the ratios of the upper limit of the therapeutic range to the mean therapeutic concentrations (mean 1.65; median 1.60; range 1.19–2.00), respectively.

Another approach has also been tested: blood concentrations of the substances detected were expressed as the proportion of the upper limit of the therapeutic range, as described in Table 1. If more than one substance were detected in one blood sample, the proportions were added up. Cases were grouped into three mutually exclusive categories (low, therapeutic, elevated concentrations). If the sum of the proportions was lower than or equal to 0.25, the case was grouped into the category "low concentrations". The threshold of 0.25 was based on the lower limit

Table 1
Therapeutic concentration range in whole blood of benzodiazepines, zopiclone and zolpidem

Substance[a]	Therapeutic concentration range (mg/L)
Alprazolam	0.02–0.03
Bromazepam + OH-Bromazepam[b]	0.08–0.17
Chlordiazepoxide	0.40–4.00
Norchlordiazepoxide	0.30–2.00
Demoxepam	0.50–0.74
Clobazam	0.10–0.40
Norclobazam	2.00–4.00
Clonazepam	0.02–0.07
Aminoclonazepam	0.02–0.07
Desalkylflurazepam	0.01–0.15
OH-ethylflurazepam	0.01–0.07
Lorazepam	0.02–0.25
Lormetazepam	0.00–0.02
Midazolam + OH-midazolam[b]	0.08–0.25
Nitrazepam	0.03–0.12
Diazepam	0.09–0.35
Nordazepam	0.01–0.47
Oxazepam	0.15–2.00
Temazepam	0.01–0.48
Zolpidem	0.08–0.30
Zopiclone	0.01–0.05

[a] Substances screened for but not detected are hydroxy-alprazolam, brotizolam, acetamidoclonazepam, acetamidonitrazepam, flunitrazepam, aminoflunitrazepam, desmethylflunitrazepam, flurazepam, ketazolam, loprazolam, desmethylmedazepam, triazolam, hydroxy-midazolam.
[b] Concentrations of the metabolite have been added to the concentration of the parent drug since therapeutic reference values for the metabolite are missing.

to upper limit ratios of the blood concentration ranges listed in Table 1 (median 0.25; mean 0.24; range 0.00–0.68). If the sum of the proportions was higher than 1, the case was grouped into the category "elevated concentrations".

2.3 Observations and results of the field sobriety tests

The field sobriety tests were focused on alertness (orientation, behavior), balance control and motor function (Romberg's test, walking, walking after turn) and ocular side effects of drugs (nystagmus, pupil size). Test observations were done by the physician who collected the blood sample or by the police officer. According to the form of request, observations with regard to walking, walking after turn and orientation were classified into the categories "not impaired", "uncertain", and "impaired". Nystagmus was classified as "negative" or "positive". Behavior was scored as "self-controlled", "unrestrained" or "sedated". Pupil size was classified into the categories "normal", "large" or "small". Romberg's test was classified as "negative", "uncertain" or "positive" (i.e. not completed or disturbed).

In practice, the information requested was not always provided. Injured drivers might not be able to perform the tests and circumstances might contribute to non-response (time of day, weather, failure to appreciate the benefits of the tests by the police or the physician). Results were classified as "not observed/not performed" if test results were missing on the form and if it was documented that the tests could not be performed. If it was not clear why observations or test results were missing on the form, the results were classified as "not documented".

2.4 Data analysis

Test results were excluded if the results of the performance tests were "not observed/not performed" or "not documented". The outcome of the tests in this study was binomial: "not impaired/uncertain" or "impaired" (walking, walking after turn, orientation), "negative" or "positive" (nystagmus), "self-controlled/unrestrained" or "sedated" (behavior), "normal" or "large or small" (pupil size) or "negative" or "positive" (Romberg's test).

A Chi square test was used to assess differences in proportions of the categorized cases.

To make the Chi square test valid for nystagmus and orientation, the subtherapeutic and the therapeutic groups were combined. A probability greater than 5% was defined to be non-significant. The relation between concentrations of benzodiazepine, zopiclone and zolpidem and performance was analyzed using SPSS 15.0 statistical software.

3. Results

3.1 Study population

In total 171 cases were included. Age and gender were documented of 169 and 136 drivers, respectively. Male drivers represented at least 53% (91/171) of the group. At least 50% (85/171) of the drivers was involved in an accident according to the information on the form of request for toxicological analysis.

3.2 Blood concentrations

Table 2 shows the substances detected in drivers suspected of driving under the influence and tested positive for benzodiazepines, zopiclone or zolpidem only. The most frequently detected benzodiazepines were oxazepam (46%; 78/171), nordazepam (37%; 64/171), temazepam (29%; 49/171) and diazepam (24%; 42/171).

3.3 Relation between blood concentration and performance

Fig. 1 shows the percentage of impaired drivers for each test within each (relative) concentration category (subtherapeutic, therapeutic, elevated concentrations of benzodiazepines). The measured blood concentrations are related to the mean of the therapeutic range, as described under methods.

Observations of behavior, walking, walking after turn and Romberg's test were significantly related to the con-

Table 2
Benzodiazepines detected in drivers suspected of driving under the influence of benzodiazepines only ($n = 171$)

Substance	n	Blood concentration (mg/L)			
		Mean	Median	Min	Max
Alprazolam	1	0.03	0.03	0.03	0.03
Bromazepam	4	0.42	0.33	0.08	0.96
OH-bromazepam	2	0.05	0.05	0.03	0.06
Chlordiazepoxide	7	2.79	0.82	0.16	11.00
Norchlordiazepoxide	5	1.21	0.63	0.34	2.68
Demoxepam	7	1.66	0.72	0.10	3.80
Clobazam	1	0.33	0.33	0.33	0.33
Norclobazam	1	1.89	1.89	1.89	1.89
Clonazepam	3	0.06	0.05	0.02	0.12
7-Aminoclonazepam	1	0.02	0.02	0.02	0.02
Flurazepam	n.d.				
Desalkylflurazepam	8	0.06	0.04	0.01	0.24
OH-ethylflurazepam	1	0.09	0.09	0.09	0.09
Lorazepam	8	0.16	0.09	0.01	0.49
Lormetazepam	7	0.03	0.02	0.01	0.05
Midazolam	4	0.05	0.05	0.02	0.09
OH-midazolam	2	0.03	0.03	0.01	0.04
Nitrazepam	3	0.08	0.10	0.01	0.12
Diazepam	42	0.33	0.22	0.01	3.00
Nordazepam	64	0.48	0.25	0.01	3.70
Oxazepam	78	0.95	0.46	0.01	7.10
Temazepam	49	0.47	0.15	0.01	2.80
Zolpidem	9	0.26	0.24	0.04	0.68
Zopiclone	3	0.15	0.09	0.05	0.30

n.d. = not detected.
Note: substances screened for but not detected are hydroxy-alprazolam, brotizolam, acetamidoclonazepam, acetamidonitrazepam, flunitrazepam, aminoflunitrazepam, desmethylflunitrazepam, flurazepam, ketazolam, loprazolam, desmethylmedazepam, triazolam, hydroxy-midazolam.

centration of benzodiazepines. A relation between the blood concentrations of benzodiazepines and pupil size, nystagmus or orientation could not be concluded.

The total number of observations for the different tests varied between 88 and 137.

The percentages of tests "not tested/not performed" (i.e. the driver was unable to perform the test) and the percentage "not documented" (i.e. information is missing) were for walking 24% (41/171) and 12% (21/171), for walking after turn 26% (45/171) and 22% (37/171), for nystagmus 12% (21/171) and 12% (20/171), for Romberg's test 29% (50/171) and 19% (33/171), for behavior 13% (23/171) and 6% (11/171), for pupils 12% (21/171) and 16% (27/171), and for orientation 16% (28/171) and 15% (26/171), respectively.

Relating the measured blood concentration to the upper limit of the therapeutic range instead of the average therapeutic concentration, yielded similar results (data are not presented).

4. Discussion

The results of our study indicate that increasing concentrations of benzodiazepines (grouped into the categories sub therapeutic, therapeutic and elevated) have an increasingly negative influence on behavior, walking, walking after turn and Romberg's test. There was no significant relation between concentration benzodiazepine and effect on pupil size, nystagmus or disturbed orientation.

Our results are for the greater part in agreement with the findings of Bramness et al. who found that 13 clinical subtests and observations for impairment were related to blood benzodiazepine concentration e.g. Romberg's test, walk and turn on line, and an observation regarding appearance.[6] However, our results did not confirm the relation between benzodiazepine concentration and orientation for time and place. A correlation between benzodiazepine concentration and performance has also been demonstrated by Kuitunen et al.[15] Their results suggest that a test battery of 13 tests was sensitive to acute benzodiazepine effects in a concentration-dependent way. Tolerance may have influenced the test results in chronic diazepam users. In addition, Longo et al. provided evidence of increased vehicle crash culpability associated with benzodiazepine use in a concentration-dependent way.[4]

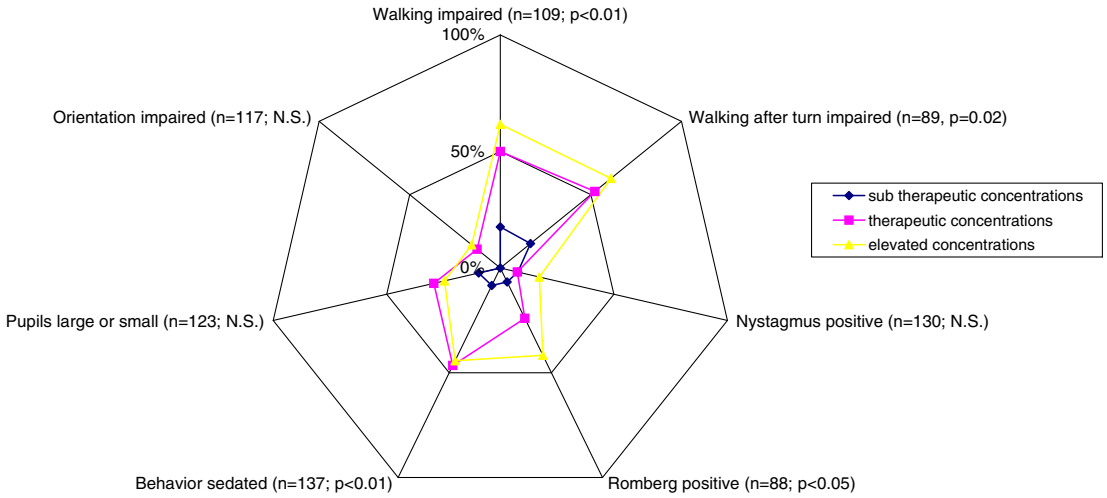

Fig. 1. The percentage of impaired drivers for the performance tests related to the relative concentrations of benzodiazepines.

The approach to summarize the benzodiazepine concentrations as described under methods, is based on the assumption that the additive effects of substances with the same pharmacological action may lead to adverse effects (e.g. impairment) even though the individual concentrations of the substances are sub therapeutic themselves. Longo et al. used a similar approach: they established a scale of benzodiazepine concentrations using the proportion of the C_{max} for standard therapeutic doses obtained from published sources (drug free, <0.26, 0.26–1.0 or >1.0). Both approaches are liable to individual differences in pharmacokinetics. Assuming that chronic use of benzodiazepines is more common than incidental use in the general driver population, classification on basis of steady state concentrations might be preferred. Bramness et al. grouped the benzodiazepines in the classes "mildly", "moderately" or "highly elevated" drug concentration levels according to clinical experience, which is expected to be in line with population based reference values published in literature. Differences can be explained by e.g. variation in prescription pattern and the comparison of plasma reference values with whole blood measurements in the clinic.

Some factors limit the conclusions to be drawn from this study. No differentiation has been made between the benzodiazepines, although it is known that benzodiazepines might differ with respect to residual effects and accident risk.[1,2,16,17] Information about chronic or single dose intake was missing although it is known that tolerance may influence test results. Another influencing factor might have been confounding by indication. Information about the case history was missing. In patients with renal failure, metabolites can accumulate, influencing the dose – concentration – effect relationship. For example, accumulation of the pharmacologically active conjugated hydroxymidazolam in serum has been described in the absence of unconjugated midazolam or hydroxymidazolam.[18] Failure rate of the standardized field sobriety tests in drivers not under the influence of psychoactive substances is unknown.

However, the predictive value of some observations and performance tests remains unclear. Friedel and Staak reviewed the literature and concluded that sedative effects of benzodiazepines were seen in several studies although subjective assessment of performance varied. Results of studies in which the influence of benzodiazepines on body sway has been examined varied from significant improvement, no significant drug effect to significant impairment.[3] Our results showed no significant effect of benzodiazepines on nystagmus nor pupil size, although literature shows that eye movements can be influenced by benzodiazepines.[19,20] Benzodiazepines have been reported to modify nystagmus, in a similar way as alcohol, and to influence saccadic movements and smooth pursuit.[20] It is not clear whether or not our results may be explained by incorrect testing by the police or the physician.

In case standardized field sobriety tests will be required to obtain a suspicion for impairment of drivers in order to justify blood sampling for evidential blood testing, they must have enough predictive value and robustness for use in varying circumstances. This does not appear to be the case. Another question is whether standardized field sobriety tests are sensitive enough to detect levels of all relevant psychoactive substances suspected to impair driving or not. Papafotiou et al. found a positive relationship between the dose of THC administered (placebo, low and high dose, respectively) and the number of healthy participants classified as impaired based on the same standardized field sobriety tests.[21,22] However, Silber et al. concluded that the horizontal gaze nystagmus test, the walk and turn test and the one leg stand test were not sensitive enough to detect the presence of low levels of amphetamine.[23]

Police officers and physicians have to appreciate the benefits of the tests in order to be motivated to perform the tests. The robustness of these tests, and as a result appreciation, can be improved by paying more attention to standardization. O'Keefe showed that a significant percentage of police surgeons in Strathclyde expressed concerns regarding the standardized field sobriety tests: the walk and turn test and the one leg stand test in particular. It has been suggested that poor performance on these tests might be related to interfering factors such as dyslexia, dyspraxia or extreme fatigue[24], which may be revealed by other tests.

5. Conclusions

The results of our study indicate a relation between the concentration of benzodiazepines (grouped into the categories sub therapeutic, therapeutic and elevated) and the influence on behavior, walking, walking after turn and Romberg's test. There was no significant relation between benzodiazepine concentration and effect on pupil size, nystagmus or orientation. The percentage of not documented test results in our study varied between 12% and 22%, indicating that the aim of the test, the performance of the test or the validity of the test may have been questioned. More effort is needed to standardize the tests in order to improve robustness and to determine the sensitivity and selectivity of the tests for the individual benzodiazepines.

Acknowledgements

The authors would like to thank the Board of prosecutors-general, police officers and research workers of the NFI for their contribution in this study.

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